# Taste and structures(1) : On the substituent effect of the nitro group and S-atom effect (preliminary report)


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# Taste and Structures I
# On the Substituent Effect of the Nitro Group and S-Atom Effect (Preliminary Report)

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## Introduction

For many years, we have studied the stereochemistry of sugars by optical properties. In those studies, the sugars that we used were sweet substances, and we confirmed the taste was changed by different substituents. Other papers have reported that the receptors indicate the differences in taste based on the preferred conformation of taste substances.

Now, we will examine the correlation between taste and conformation that we have studied. First, we synthesized the taste substances having a nitro group and a Sulfur atom, then we checked the taste. In order to evaluate the tastes, the following compounds (*1*～*11*) were employed as shown in Fig. 1.

## Experimental

The samples were prepared according to the methods described in the literature. The others except *4* were also synthesized in similar ways. The structures of all compounds were confirmed by the infrared spectra and comparison of melting points. Melting points are uncorrected. Compound *4* was of commercial origin by Sigma Chem. Co.

Phenyl β-D-Glucopyranoside (*1*)[1-3]. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (***a***) was synthesized by the bromination of 1, 2, 3, 4, 6-penta-*O*-acetyl-α-D-glucopyranoside followed by the acetylation of D-glucose with acetic anhydride. Compound *1* was obtained by the hydrolysis of phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside with sodium methoxide followed by the reaction of compound ***a*** with phenol. Colorless needles; mp 171-172°C.

*o*-Nitrophenyl β-D-Glucopyranoside (*2*)[3]. This was synthesized by the method similar to compound *1* using *o*-nitrophenol instead of phenol. Yellow crystals; mp 198°C.

*p*-Nitrophenyl β-D-Glucopyranoside (*3*)[3]. This was synthesized by the method similar to compound *1* using *p*-nitrophenol instead of phenol. Colorless needles; mp 163°C.

*p*-Nitrophenyl 1-Thio-β-D-Glucopyranoside (*4*). Colorless needles; mp 159°C.

6-Nitrosaccharin (*5*)[4]. 5-Nitro-*o*-toluene sulfamide (***b***) was synthesized by the reaction of *p*-nitrotoluene with chlorosulfonic acid and ammonia water. Compound *5* was obtained by the cyclization with chromium trioxide of compound ***b***. Yellow crystals; mp 212°C.

1-(β-Carboxyethyl)-3-Phenylurea (*6*)[5,6]. This was synthesized from the reaction of β-alanine and phenyl isocyanate. Colorless needles; mp 101-103°C.

1-(β-Carboxyethyl)-3-*p*-Nitrophenylurea (*7*)[5,6]. *p*-Nitrobenzoyl azide (***c***) was obtained by the reaction of *p*-nitrobenzoyl chloride with sodium azide. *p*-Nitrophenyl isocyanate (***d***) was obtained by heating compound ***c*** with the generation of nitrogen. Compound *7* was synthesized by the reaction of compound ***d*** and β-alanine. Yellow crystals; mp 185-187°C.

1-(β-Carboxyethyl)-3-phenylthiourea (*8*)[5,6]. Phenyl isothiocyanate was obtained by the reaction of carbon disulfide and aniline. Compound *8* was synthesized by the reaction of phenyl isothiocyanate with β-alanine. Colorless crystals; mp 113-115°C.

1-(β-Carboxyethyl)-3-*o*-Nitrophenylthiourea (*9*)[5,6]. *o*-Nitrophenyl thioisocyanate (***e***) was prepared by the reaction of *o*-nitroaniline with thiophosgene. Compound *9* was obtained by the reaction of compound ***e*** with β-alanine. Slightly yellow crystals; mp 96-100°C.

1-(β-Carboxyethyl)-3-*m*-Nitrophenylthiourea (*10*)[5,6].

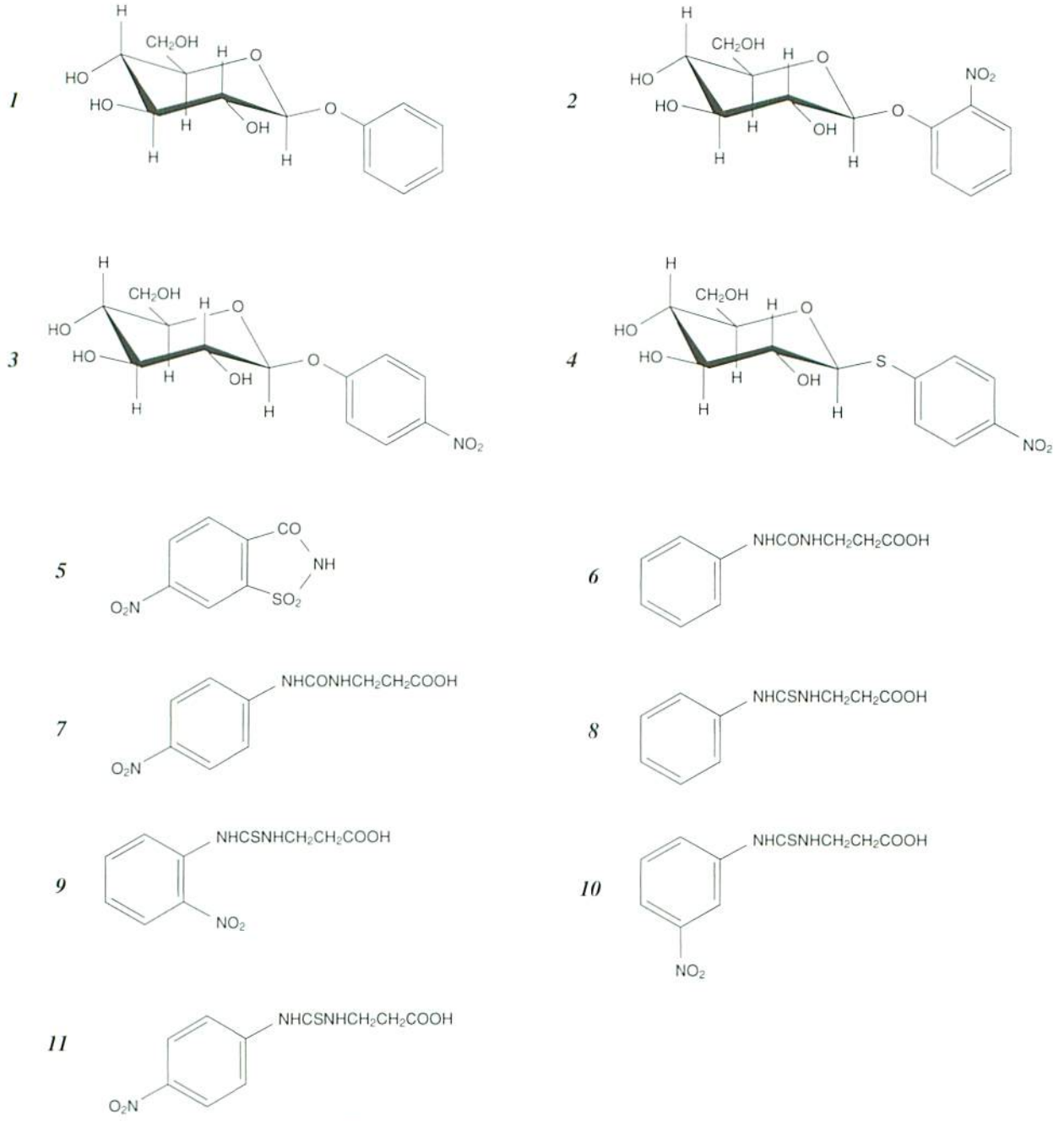


Figure 1. Compounds *1*～*11* examined.

*m*-Nitrophenyl thioisocyanate (*f*) was obtained by the reaction of *m*-nitroaniline and thiophosgene. Compound *10* was obtained by the reaction of compound *f* and β-alanine. Slightly yellow crystals; mp 167-169°C.

1-(β-Carboxyethyl)-3-*p*-Nitrophenylthiourea (*11*)[5,6]. *p*-Nitrophenyl thioisocyanate (*g*) was obtained by the reaction of *p*-nitroaniline with thiophosgene. Compound *11* was obtained by the reaction of compound *g* with β-alanine. Pale yellow needles; mp 151-152°C.

## Results and Discussion

The taste was investigated with the researchers' tongues because taste receptors are located in taste buds found in the tongue.

It is known that β-D-glucose sweetness relative to sucrose is 0.82[7], but phenyl β-D-glucoside (*1*) tasted

only of bitterness without any sweetness. In the case of compound *2*, which introduces the nitro group to the *ortho*-position of the phenyl group in compound *1*, the bitterness increases a little bit compared to compound *1*. However, in the case of compound *3*, which introduces the nitro group to the *para*-position of the phenyl group in compound *1*, the taste of bitterness increases dramatically. *p*-Nitrophenyl 1-thio-$\beta$-D-glucopyranoside (*4*) which substituents an O atom with an S atom at $C_1$ tastes slightly sweet then bitter. The order of bitterness is *3*>*2*>*1*>*4* as seen in Table 1.

It has been reported[8,9] that in the case of saccharin, when a substituent is introduced to the phenyl group, it increases in bitterness and, especially in the case of the 6-nitrophenyl group, saccharin is changed to a bitter substance. In order to investigate this bitterness, it was synthesized from the *p*-nitrotoluene as starting material. When we checked the taste of compound *5*, it tasted a little sweet for a short time, then strongly bitter. Both of the tastes are stronger than compound *4*. As for glucose derivatives *1*~*4* and saccharin derivative *5*, substitutions in the phenyl group with the electron-withdrawing nitro group produce a bitter tasting substance.

Meanwhile, it is reported[9,10] that phenylurea derivative (*6*) tastes only weakly sweet but compound *7*, which introduced the nitro group to $C_6$ in the phenyl group of compound *6*, tastes 350 times sweeter. In order to investigate the effect of the nitro group, 1-($\beta$-carboxyethyl)-3-phenylurea (*6*) without $NO_2$ and 1-($\beta$-carboxyethyl)-3-*p*-nitrophenylurea (*7*) having $NO_2$ were synthesized. The tastes of these compounds are listed in Table 1. By examining Table 1, the tendency of tastes of compounds *6* and *7* is completely different from glucose (*3*) and saccharin (*5*). Therefore, the introduction of the nitro group to the phenylurea contributes to the strong sweetness.

Table 1. Taste of Substances Having Phenyl Group

| Compound No. | Taste |
|---|---|
| *1* | moderately bitter |
| *2* | bitter |
| *3* | very bitter |
| *4* | slightly sweet then very bitter |
| *5* | slightly sweet then strongly bitter |
| *6* | faintly sweet |
| *7* | strongly sweet |
| *8* | sweet |
| *9* | sweet but not immediately |
| *10* | sweet and bitter after a short time |
| *11* | strongly sweet |

Moreover, in order to investigate the effect of sweetness in the case of introducing an S atom, the phenylthiourea derivative (*8*) and the *o*- (*9*), the *m*- (*10*) and the *p*- (*11*) nitro derivatives of *8* were synthesized. Compound *8* is the substance that changed C=O of compound *6* to C=S. Compound *8* tastes sweet and this sweetness is stronger than compound *6*, but compound *8* has a little bitterness following the sweetness. That means the sulfur atom contributes to the sweetness. The 1-($\beta$-carboxyethyl)-3-*o*-nitrophenylthiourea (*9*) that is the *ortho*-nitro derivative of compound *8* tastes the same as compound *8*, but compound *9*'s sweetness is weaker and its bitterness is stronger than compound *8*. The 1-($\beta$-carboxyethyl)-3-*m*-nitrophenylthiourea (*10*) that is the *meta*-isomer of compound *9* tastes the same as compound *9*, but compound *10*'s sweetness is weaker and its bitterness is stronger than compound *9*. Finally, the 1-($\beta$-carboxyethyl)-3-*p*-nitrophenylthiourea (*11*) that is the *para*-isomer of compound *10* tastes sweeter than compound *8* and slightly bitter. Compound *11* is the substance that changed C=O of compound *7* to C=S. That confirms the strong influence the S atom has on sweetness. All results are shown in Table 1. By comparing the sweetness of thiourea derivatives, the sweetness scale is *11*>*8*>*9*>*10* and the bitterness that appears after sweetness is the reverse of the sweetness scale.

Next, the minimizing energy of MOPAC computations were performed on glucosides (*1*~*4*). The conformations of each molecule are shown in Figure 2. As reported earlier, the order of bitterness is *3*>*2*>*1*>*4* with compound *4* showing signs of sweetness. In Figure 2, we can see that while compounds *1*~*3* have a trans-type form between the glucoside rings and the benzene rings, compound *4* shows a cis-type form. The cis-type and trans-type forms affect different acceptors in the taste buds of our tongues. So, we think that is why compound *4* is the only one that has a bit of sweetness.

As for compounds *5*~*11*, we stated earlier that: 1. the *para*-nitro group introduced the strong sweetness; and 2. S-atom contributed more sweetness than the O-atom.

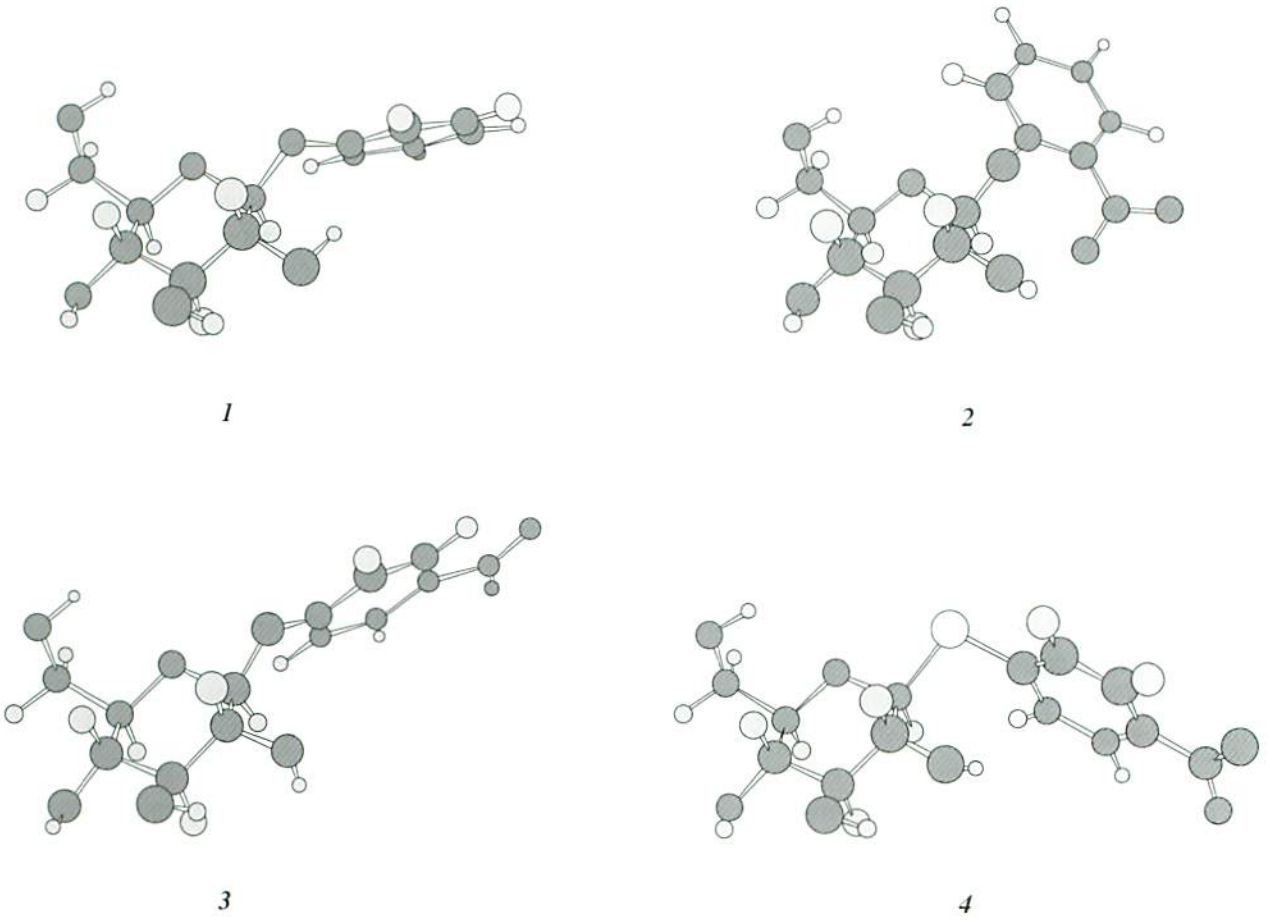


Figure 2. MOPAC Computations Models of *1*～*4*

All conformations of compounds *5*～*11* by MOPAC computations were obtained but did not show significant differences. In these cases, it is effective to apply the AH-B theory proposed by Shallenberger *et al.*[11,12] in order to explain the difference between the taste.

This time we determined the relative sweetness and bitterness of the substances by using our tongues only. We have plans to measure the threshold by statistical analysis.

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